

REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 2, 4, 6, 9, 10, 12, 14, 25, and 26 are under consideration. Claims 25 and 26 are newly added to clarify antibodies of the invention. Support for the new claims can be found, as an example, on page 21, lines 19-28.

No new matter is added.

The claims herewith are patentably distinct over the prior art and these claims are in full compliance with the requirements of 35 U.S.C. § 112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that these amendments should not give rise to any estoppel, as they are not narrowing amendments.

II. THE REJECTIONS UNDER 35 U.S.C. § 112 ARE OVERCOME

Enablement

Claims 1, 2, 4, 6, 9, 10, 12, and 14 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the specification does not provide enablement for a method of modulating T-cell activation or proliferation comprising administering T-cells with a modulator of a Hedgehog signalling pathway or a modulator of a pathway which is a target of the Hedgehog signalling pathway. The rejection is traversed.

The Examiner conceded that the general activation of T-cells in response to antigens does not require administration of anti-CD3 or anti-CD28 antibodies since T-cell activation via CD3 and CD28 is apart of ongoing immune responses; however, the Examiner asserted that the claims are not limited to an *in vivo* treatment setting and thereby does not provide guidance on how to use the Shh protein as a modulator of activation of isolated T-cells in the absence of anti-CD3 and anti-CD28 antibodies.

In response, Applicants argue that one skilled in the art can practice the present invention in an *in vitro* treatment setting without undue experimentation. As noted in MPEP Section

2164.02, “[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed.” Hence, even though the Examiner does not consider there to be an example of the *in vitro* use the Shh protein as a modulator of T-cell activation in the absence of anti-CD3 and anti-CD28 antibodies, the guidance provided in the specification for *in vitro* application of the present invention sufficiently enables one skilled in the art to use the Shh protein as a modulator of T-cell activation *in vitro*. For instance, the specification describes the Shh protein (page 16, line 12 – page 17, line 8) and methods for isolating T-cells (page 91, Example 3), and application of the Shh protein is well within the skill of one in the art. With this in mind, the skilled artisan can practice the present invention in an *in vitro* treatment setting without undue experimentation.

The Examiner also alleged that the claims lack enablement for the full scope of upregulators encompassed by the claims. The Examiner contended that the specification only provided guidance for Smo and Gli, which are significantly different than Shh in function.

In response, Applicants assert that it is well within the skill of one in the art to practice the upregulators of the invention. As described previously, the specification provides numerous examples of various upregulators (see page 18, line 28 – page 22, line 18), as well as assays that can be used to confirm activity of any particular upregulator (see page, 22, line 19 – page 23, line 17). Even if the skilled artisan must perform an assay as amply described in the specification, Applicants further note that “an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance.” *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Considering that the specification indeed provides sufficient direction and guidance for the upregulators of the present invention and how their activity may be assessed, the upregulators encompassed by the present claims are enabled.

Finally, the Examiner alleged that the claims are not enabled for a method of modulating T-cell activation *in vivo*. The Examiner contended that the specification does not provide any working examples, and that the relevant art suggests that the skilled artisan could not predict whether or not administration of Shh or a modulator of Shh signalling pathway would result in an increase, decrease, or no effect on T-cell activation or proliferation.

In response, Applicants argue that the specification provides substantial guidance for practicing the present invention *in vivo*. As noted previously, the specification amply describes the form, route, and dosage of modulators of the invention (see “Methods of Delivery” beginning

on page 80, line 26, and “Administration” beginning on page 83, line 5). Furthermore, Applicants refer to MPEP Section 2164.02, which states that “[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a ‘working example’ if that example ‘correlates’ with a disclosed or claimed method invention.

In this case, the examples of applying modulators to isolated T-cells from specification, most notably Example 13, correlates to the instant claims, which encompasses *in vivo* methods of treatment. In fact, the Examiner indicated in the Office Action (paragraph bridging pages 3 and 4) that Example 13 demonstrates a correlation to an *in vivo* setting by admitting that the administration of anti-CD3 or anti-CD28 antibodies mimics an ongoing immune response. Hence, the instant claims are enabled for an *in vivo* method of modulating T-cell activation,

In view of the arguments above, Applicants assert that the skilled artisan can clearly practice the claimed invention without undue experimentation. Reconsideration and withdrawal of the enablement rejection are requested.

Written Description

Claims 1, 2, 4, 6, 9, 10, 12, and 14 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is traversed.

The Examiner alleged that the specification only specifically discloses examples of such agonists as Smo and Gli, but that the skilled artisan would not consider these compounds to represent the compounds that could be used with the claimed methods; according to the Examiner, there is no description of a method wherein T-cells are contacted with the Smo receptor or the Gil protein to result in T-cell activation or proliferation.

In response, Applicants reminds the Examiner that the presence of working examples demonstrating the use of Smo receptor or the Gil protein is not necessary so long as the Applicants demonstrate possession of the claimed invention at the time of the filing date. To this end, Applicants point to the substantial description of the Smo receptor or the Gil protein in the specification (for example, pages 15, line 19 – page 16, line 20) and to the demonstration of using modulators to affect T-cell activation and proliferation (Example 13). Hence, Applicants were clearly in possession of Smo receptor and the Gil protein as modulators of the present invention.

The Office Action also alleged that the genus of upregulators encompassed by the present invention is highly variant and that there is no description of which modulators of the hedgehog signalling pathway are upregulators.

In response, Applicants assert that the Hedgehog signaling pathway (page 15, line 12 – page 18, line 7), as well as a representative number of species of upregulators of a Hedgehog signaling pathway (page 18, line 28 – page 22, line 18), are well-described in the specification. Applicants further assert that a large number of modulators that can upregulate Shh signalling are known in the art, including the proteins and non-protein organic molecules described in the specification. Taken together, it would be clear to a skilled artisan which modulators can be used as upregulators of the present invention.

Accordingly, the subject matter of the instant claims is sufficiently supported by the specification. Reconsideration and withdrawal of the rejection are requested.

III. THE REJECTIONS UNDER 35 U.S.C. § 102 ARE OVERCOME

Claims 1, 2, 4, 6, 9, 10, 12, and 14 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Van Gool *et al.* (Journal of Immunology 150: 3254-3263, 1993). According to the Examiner, Van Gool *et al.* relates to a method of contacting T-cells with sub-optimal doses of anti-CD3 and anti-CD28 antibodies, which would inherently activate T-cells to secrete Shh. The Examiner contended that placing T-cells into culture plates as described in Van Gool *et al.* meets the definition of “administer” as recited in the instant claims. The rejection is traversed.

Applicants disagree that Van Gool *et al.* relates to the administration of a modulator to T-cells. The Examiner turns to the definition of administer as “to make application; give.” In the case of Van Gool *et al.*, the modulator, *i.e.*, the anti-CD3 and anti-CD28 antibodies, are not being “applied” or “given” to T-cells, but rather the T-cells are being placed on into culture plates coated with the anti-CD3 and anti-CD28 antibodies. The specification provides examples of “administration” of the modulators of the invention (page 83, line 4 – page 86, line 29) which are clearly different than the methods of Van Gool *et al.* Thus, Van Gool *et al.* does not anticipate the present invention.

Claims 1, 2, 4, 6, 9, 10, 12, and 14 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Outram *et al.* The Examiner asserted that Outram *et al.* relates to culturing thymocytes with an anti-Hh neutralizing antibody, which increased thymocyte differentiation. The Examiner contended that the recitation of “modulating T-cell activation” or “modulating T-

cell proliferation” in the preamble relates to intended use and bears no accorded patentable weight. The rejection is traversed.

Applicants point to MPEP Section 2111.02 which states that “[t]he claim preamble must be read in the context of the entire claim.” Further, “the preamble is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed.” *In re Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158. For example, “[i]n a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to ‘a human in need thereof’ ... the claim is properly interpreted to mean that the vitamin preparation must be administered to a human with a recognized need to treat or prevent pernicious anemia.”

With this in mind, the instant claims are recognized as being directed to a method of “modulating T-cell activation” or “modulating T-cell proliferation,” and that cited references must teach a method of modulating T-cell activation or modulating T-cell proliferation in order to be considered as anticipatory prior art. Clearly, Outlam *et al.*, which relates to thymocyte development, does not relate to T-cell activation or proliferation as recited in the instant claims.

Claims 1, 2, 4, 6, 9, 10, 12, and 14 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Stewart *et al.* The Examiner contends that Stewart *et al.* relates to a study wherein the addition of recombinant Shh peptide enhanced proliferative response of both CD4+ and CD8+ cells following stimulation with α CD3 and α CD28. The rejection is traversed.

Applicants note that Stewart *et al.*, while merely relating to T-cell proliferation, does not teach this limitation. Moreover, Stewart *et al.* only recites that the addition of Shh enhances the proliferative response, and the cited reference does not provide enough information to be considered as an enabling disclosure. Applicants remind the Examiner that a reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. See *In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985). In this case, the teachings of Stewart *et al.* is insufficient.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) are requested.

CONCLUSION

This application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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